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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/692,084	08/08/96	RODRIGUEZ M	1199-1-001-C

HM12/0316

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EXAMINER	
DUFFY,P	

ART UNIT	PAPER NUMBER
1645	15

DATE MAILED: 03/16/99

Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/692,084	Applicant(s) Rodriguez et al
	Examiner Duffy	Group Art Unit 1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 12-10-98.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-19 is/are pending in the application.

Of the above claim(s) 5-8, 15-18 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-4, 9-14 and 19 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claim(s) 1-19 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

Response to Amendment

1. The amendment filed 12-10-98 has been entered into the record. Claims 1-4, 9-14 and 19 are under examination.

2. This application contains claims 5-8 and 15-18 drawn to an invention nonelected with traverse in Paper No. 7. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Maintained

Double Patenting

4. The rejection of claim 19 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1 of prior U.S. Patent No. 5,591,629 this is a double patenting rejection is maintained inasmuch as applicant has acknowledged this rejection (see top of page 3 of response) but has failed to traverse the rejection.

Applicants allege that they will file a terminal disclaimer when appropriate. It is noted that a rejection under 35 U.S.C. 101 can not be overcome by a terminal disclaimer.

Claim Rejections - 35 USC § 102 or 103

Priority Date Assigned Claimed Invention

5. The rejection of claims 1-4, 9 and 11-14 under 35 U.S.C. 102(b) as being anticipated by Miller et al (J. Neurosci., 14:6230-6238, 1994) is maintained for reasons made of record in Paper No. 9, mailed 10-2-97.

Applicants state that the instant claims are indeed entitled to the priority date of the parent application and provide citations of passages from the parent which has issues as US Patent No., 5,591,629.

Applicants point to column 2, for written description for SCH 94.03, column 8, for O4 and A2B5 and column 9 for isolated or synthetic autoantibodies. This is not persuasive because there is no conception of the use of antibodies 04 or A2B5 in the treatment method, nor any indication in these passages that these antibodies have the property of stimulating remyelination of central nervous system axons or could be used to treat a demyleinating disease and thus their use as pharmaceutical agents does not logically flow from the cited passages. Citation of use of the antibodies to characterize and antigen does not provide written description support for the use of the antibody as a pharmaceutical agent in the methods as instantly claimed. The passages cited by applicants do not provide for the use of the antibodies in the methods and pharmaceutical compositions claimed nor does it logically flow from the specification. Applicants' attempt to rely antibodies discussed in prior art references but have no written description in the priority document specification as originally filed as argued for 01 and HNK-1 is not persuasive. It is the parent specification that must provide written description, not references cited therein. These alleged references have not been properly incorporated by reference, nor does the specification of the parent document point to these specific antibodies for use as therapeutic agents for stimulating remyleination. As to passage for isolated or synthetic autoantibodies, the passage again not conceptualize the use of isolated or synthetic antibodies in

a method of treatment and provides no written description for synthetic autoantibodies and merely discusses the background of the art and not specific isolated or synthetic autoantibodies.

Priority to the parent document for the instantly claimed Markush is denied. The rejection is maintained.

Claim Rejections - 35 USC § 112

6. The rejection of claims 1-4, 9-14 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of stimulating remyelination or treating a demyelinating disease in a mammal by administering to a mammal an effective amount of the monoclonal antibody A2B5, it does not reasonably provide enablement for, isolated or synthetic autoantibodies or treatment of a demyelinating disease in mice or humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims is maintained for reasons made of record in Paper No. 9, mailed 10-2-97.

Applicants arguments have been carefully considered but are not fully persuasive. Applicants have not yet established the unrestricted public availability of 01 and 04. Applicants indicate that evidence should be forthcoming. This part of the rejection is maintained until such time as persuasive evidence is provided. Applicants allege that the antibody HNK-1 is publicly available and provides pages from the ATCC catalogue. This is not persuasive, the availability is not unrestricted and the catalogue for the antibody HNK-1 states "This material is available under the conditions that you will not use it for commercial purposes or distribute it to third parties.". Thus, this hybridoma and monoclonal antibody is *not freely commercially available to the public, it has access restrictions*. Thus, the antibody HNK-1 antibody is not compliant because *all*

restrictions upon the availability to the public of the deposited biological material has not been granted by the ATCC, this HNK-1 is not compliant because the ATCC catalogue clearly and unambiguously states that its' *access is restricted.*

Applicants allege that the examiner has conceded that the specification is enabled for making and using isolated or synthetic autoantibodies. The examiner has never conceded that polyclonal antibodies such as isolated or synthetic autoantibodies are enabled for reasons previously made of record.

> Applicants' assert *In re Fisher* 427 F.2nd 833, 839, 166 USPQ 18, 24 (CCPA 1970) in that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement would be met. The evidence now submitted by applicants as Appendix C enables the scope of the claims 1-4, 9-14 19 for antibodies SCH 94.03, SCH 97.08, O1, O4, A2B2, HNK-1, antigen binding fragments thereof, ***provided that the deposit issues are appropriately settled, however it does not provide support for isolate or synthetic autoantibodies having the characteristics thereof for the reasons set forth below.*** The evidence does not support isolated polyclonal antibodies such as autoantibodies or synthetic autoantibodies. Provided that deposit requirements are met, claims drawn to the scope set forth directly above would be allowable, in view that promotion of central nervous system remyelination stabilizes disease as set forth in the specification (pages 20-21) and the other antibodies which have been demonstrated to promote central nervous system remyelination would be expected to be similarly effective and that the demonstration of therapeutic effectiveness was demonstrated in the Theiler's Virus-Induce Demyelinating Disease model and not the EAE mouse which has been demonstrated to lack predictable correlation with effective treatment in human disease.

As to isolated or synthetic autoantibodies, the specification fails to teach how to make isolated or synthetic autoantibodies with the characteristics of the monoclonal antibodies of the claims. The specification fails to teach from which animal these autoantibodies can be isolated. Autoantibodies are generally polyclonal and not monoclonal in nature. The population of autoantibodies from one outbred animal to another differs because the antibody genetic repertoire differs. Thus, the specification fails to teach how to predictably and reproducibly make a polyclonal antibody with the characteristics of the monoclonal antibody. Moreover, the art teaches that making polyclonal antibodies is unpredictable. The art specifically teaches that the production of polyclonal antiserum is variable and not readily reproducible. Autoantibodies are innately a polyclonal antibody population Campbell et al (page 3, column 2) teach that:

> "Polyclonal antiserum consists of a wide variety of antibody molecules of different specificity and affinity (Fig. 1.1). Each time an animal is bled, it yields a different 'cocktail' of such antibodies as its immune response to the injected and environmental antigen alters and B cell clones emerge and recede. The same animal can yield a highly specific

> antiserum directed against the chosen antigen in one bleed and a poor antiserum in another . The animal also has a limited lifespan and prior to the days of Mab technology, the death of a single rabbit could cause major problems is a diagnostic laboratory.
>
> There is an additional inter-animal variability among animals which cannot readily be inbred in the same way as small rodents can be inbred to yield pure strains with matching histocompatibility antigens (Section 3.4). While large 'outbred' animals such a s rabbits, sheep and goats, can yield a large quantity of specific antibody, their response to antigen is variable and it was often necessary to immunise up to 30 animals to obtain a high-affinity antiserum."

Applicants argue that the specification teaches how to make isolated or synthetic autoantibodies and points to pages 7-11 by using conventional methods. Conventional methods utilize antigen immunization and no antigen is described in any sufficient manner in order to be able to make isolated autoantibodies or synthetic autoantibodies by any conventional methodology in the art. This is also not persuasive because the passage cited by applicant does not define isolated autoantibody or synthetic autoantibody as an engineered or manipulated antibody as alleged. The term is given its broadest reasonable interpretation of the art. The broadest interpretation of autoantibody is an isolated polyclonal antibody or synthetic polyclonal antibody, neither of which is enabled for reasons already made of record. Given the evidence provided by the examiner and that the specification does not teach provide any evidence that the instantly claimed antibodies can predictably and reproducibly made as asserted using conventional technology which have the property of capable of inducing remyelination of central nervous system axons. Applicants argue that the generation of polyclonal antibodies are the first step in the generation of monoclonal antibodies, while this may be true for classical production of monoclonal antibodies using antigen injection it is not true in view of the teachings of the specification. The monoclonal antibodies of the specification were not sensitized to any antigen, but were apparently developed from immortalized splenocytes in the absence of any antigen immunization. Thus, the production of monoclonal antibodies is not preceed by polyclonal antibody generation

according to methods of making monoclonal antibodies of the specification. The specification teaches how to screen for monoclonal antibodies and does not teach how to make or screen for isolated polyclonal autoantibodies or synthetic polyclonal antibodies with the instantly claimed properties. Applicants allege that the specification teaches animal models which are susceptible to demyelinating disease and others are demyelination refractive, it would be readily clear to one of skill in the art as to which animals to use to generate such autoantibodies. This is not persuasive, the courts have held that:

> "However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It meas that the omission of minor detains does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material *or of any conditions under which a process can be carried out,* [emphasis added] undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research." (Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001).

In the instant case there is no disclosure of antigen for which isolated or synthetic polyclonal autoantibodies may generated nor any specific animals which generate autoantibodies with the remyelinating properties, undue experimentation is required.

The specification remains not enabled for isolated polyclonal (autoantibodies) or synthetic autoantibodies which are capable of inducing remyelination of central nervous system axons and the rejection is maintained.

Status of Claims

7. All claims stand rejected.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

9. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995.

Patricia A. Duffy, Ph.D.
March 14, 1999

Patricia A. Duffy, Ph.D.
Primary Examiner

Group 1600